REMARKS

I. Claims in the Case

New claim 42 has been added. Claims 1, 36, 39 and 41 have been amended. Claims 1-42 are pending of which claims 17-19, 22-28, 33 and 34 are withdrawn. Claims 1-16, 20-21, 29-32 and 35-42 are under examination.

II. Rejection of Claims – Enablement

The Action first rejects all the claims on the basis of enablement on various bases, the first of which appears to be that the specification does not provide any guidance as to how transgenic fish in species other than zebrafish would be made.

In response, Applicants first note that many, many different species of fish have now been genetically engineered such that now the genetic engineering of fish is generally routine. This is noted in the present specification at paragraph 5:

> [0005] Fish are also an intensive research subject of transgenic studies. There are many ways of introducing a foreign gene into fish, including: microinjection (e.g. Zhu et al., 1985; Du et al., 1992), electroporation (Powers et al., 1992), sperm-mediated gene transfer (Khoo et al., 1992; Sin et al., 1993), gene bombardment or gene gun (Zelemin et al., 1991), liposome-mediated gene transfer (Szelei et al., 1994), and the direct injection of DNA into muscle tissue (Xu et al., 1999). The first transgenic fish report was published by Zhu et al. (1985) using a chimeric gene construct consisting of a mouse metallothionein gene promoter and a human growth hormone gene. Most of the early transgenic fish studies have concentrated on growth hormone gene transfer with an aim of generating fast growing "superfish". A majority of early attempts used heterologous growth hormone genes and promoters and failed to produce gigantic superfish (e.g. Chourrout et al., 1986; Penman et al., 1990; Brem et al., 1988; Gross et al., 1992). But enhanced growth of transgenic fish has been demonstrated in several fish species including Atlantic salmon, several species of Pacific salmons, and loach (e.g. Du et al., 1992; Delvin et al., 1994, 1995; Tsai et al., 1995).

Furthermore, this fact has been recognized by the US PTO in several issued US patents that are presumptively fully enabling. For example, Applicants make reference to Cooper *et al.*, US 5,998,698. This patent is directed to transgenic fish that are capable of expressing heterologous

lytic peptides. This patent provides a detailed disclosure of the preparation of numerous species of transgenic fish, including any bony fish, exemplified by catfish and koi. Note that the claims of this patent cover any transgenic bony fish. Similarly, Winn *et al.*, US 6,307,121, discloses and claims the preparation of any transgenic fish species, including cartilagenous fish, for mutation detection. Please see the first several paragraphs of the Detailed Description section, as well as the claims. Furthermore, we would direct the Examiner's attention to Winn, US 6,472,583, which similarly discloses and claims the preparation of any species of transgenic fish, again for mutation detection. These patents are presumptively enabling for the preparation of any transgenic fish.

The evidence put forward by the Examiner does not support the position of non-enablement. The relevance of the Betancourt *et al.* reference is not at all understood, as this reference, which is of limited relevance anyway due to the fact it is very old, actually supports enablement. Betancourt *et al.* merely stands for the proposition that non-fish regulatory elements such as promoters do not work *as well* in fish cells as fish regulatory elements. It does not state that such regulatory elements lack utility in fish, they simply do not work *as well.* Indeed, the abstract states that the CMV promoters and RSV promoters, which are both viral, non-fish, promoters, "were the most potent in all cell types." Note that the excerpt relied upon by the Examiner merely states that transgenic fish cells "should preferably contain" DNA sequences from fish genes – not that *only* fish elements will work. This reference actually demonstrates the level of skill in the art only as of 1993, and shows that even then those of skill were well aware that fish promoters and elements were preferred but not the only elements that would function.

The Bearzotti *et al.* reference is similarly very old and outdated (1992), but again actually supports enablement. It is noted that this reference shows that the CMV, RSV and even the

heat-inducible human HSP-70 promoters functioned well in fish cells. Again, the excerpt relied on by the Examiner merely indicates that certain elements may not function as efficiently as others. The fact that something "does not work as well", does not lead to the conclusion that the present invention is not enabled for the preparation of any transgenic fish using any promoter.

The same can be said for Higashijima *et al.*, which again merely stands for the proposition that those of skill in the art were aware that certain design choices may need to be made in order to achieve an optimally performing transgenic fish. This is not a proper basis for raising an enablement concern.

Indeed, the very art reference cited by the Examiner, Higashijima *et al.*, fully evidences the broad knowledge in the art for making fluorescent transgenic fish have a variety of elements and promoters.

We would also refer the Examiner to various articles of record. For example, the Examiner is referred to Kuo *et al.*, reference C45, which demonstrates that cis-acting elements from mouse carcinoma nectin neurofilament gene were effective in directing either neuron-specific or skin-specific expression (depending on the particular construct) in zebrafish. See also, Kim *et al.*, reference C44.

The Examiner is further referred to Moss *et al.*, reference C54, which demonstrates the ability of a rat myosin promoter to direct muscle specific expression in zebrafish.

Lastly, the Examiner is referred to the enclosed review article of Hackett *et al.*, "The Molecular Genetics of Transgenic Fish," which was published in 2000 at about the same time as the filing of the present application. This review article sets forth an abundance of non-fish tissue specific and other promoters that were all routinely found to be operable in fish. See, for example, Tables 1 through 3.

Accordingly, it is submitted that the Examiner has failed to make a prima facie case of non-enablement. Further, Applicants have presented substantial evidence in support of broad enablement. Accordingly, the Examiner is requested to withdraw the rejection.

III. Rejection of Claims – Written Description

The Action next enters a written description rejection of all of the claims on the basis that the specification is said not provide an adequate written description of useful tissue specific promoters beyond the MLC2 promoter and the MCK promoter. Notably, no evidence is provided in support of the rejection.

In response, it is first noted that there is no legal basis under the written description requirement that an applicant set forth in the claims the specific structures being claimed where, as here, the *class* of compounds being claimed are known to the prior art. Instructive in this regard is the Federal Circuit's recent decision in *Capon v. Eshhar v. Dudas*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005). As the *Capon* court points out, there is no requirement under written description that a specification contain a detailed description of elements where those elements are well known to those in the field:

> The Board stated that "controlling precedent" required inclusion in the specification of the complete nucleotide sequence of "at least one" chimeric gene. Bd. op. at 4. The Board also objected that the claims were broader than the specific examples. Eshhar and Capon each responds by pointing to the scientific completeness and depth of their descriptive texts, as well as to their illustrative examples. The Board did not relate any of the claims, broad or narrow, to the examples, but invalidated all of the claims without analysis of their scope and the relation of claim scope to the details of the specifications.
>
> Eshhar and Capon both argue that they have set forth an invention whose scope is fully and fairly described, for the nucleotide sequences of the DNA in chimeric combination is readily understood to contain the nucleotide sequences of the DNA components. Eshhar points to the general and specific description in his specification of known immune-related DNA segments, including the examples of their linking. Capon points similarly to his description of selecting DNA segments that are known to express immune-related proteins, and stresses the existing knowledge of these segments and their nucleotide sequences, as well as the

known procedures for selecting and combining DNA segments, as cited in the specification.

Both parties argue that the Board misconstrued precedent, and that precedent does not establish a *per se* rule requiring nucleotide-by-nucleotide re-analysis when the structure of the component DNA segments is already known, or readily determined by known procedures. The "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. See *Enzo Biochem*, 296 F.3d at 1330 (the written description requirement "is the *quid pro quo* of the patent system; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time"); *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46 (Fed. Cir. 2000) (the purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification"); *In re Barker*, 559 F.2d 588, 592 n.4 (CCPA 1977) (the goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed"). The written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity.

The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for

each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

For the chimeric genes of the Capon and Eshhar inventions, the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e.*, *Regents v. Lilly*, *Fiers v. Revel*, *Amgen*, or *Enzo Biochem*, require a re-description of what was already known. In *Lilly*, 119 F.3d at 1567, the cDNA for human insulin had never been characterized. Similarly in *Fiers*, 984 F.2d at 1171, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a "wish" or research "plan." In *Amgen*, 927 F.2d at 1206, the court explained that a novel gene was not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In *Enzo Biochem*, 296 F.3d at 1326, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen Inc. v. Hoechst*

Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) the court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." These evolving principles were applied in *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004), where the court affirmed that the human antibody there at issue was not adequately described by the structure and function of the mouse antigen; and in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925-26 (Fed. Cir. 2004), where the court affirmed that the description of the COX-2 enzyme did not serve to describe unknown compounds capable of selectively inhibiting the enzyme.

The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.

The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern the discovery of gene function or structure, as in Lilly. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

The Capon case has very recently been followed by the Federal Circuit, in *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006). In a section of the opinion entitled "Recitation of Known Structure Is Not Required" the *Falkner* court, following the *Capon* decision, stated:

Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a

> person of ordinary skill in the art that the patentee was in possession of the claimed invention. ... Accordingly, we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences.

Id. at 1008.

The fact that tissue specific promoters were exceedingly well known as of the filing date is evidenced by evidence set forth above in the enablement section of this response.

Thus, it is submitted that there is clearly no *prima facie* basis for subject written description rejection, and that Applicants have provided evidence in support of written description. For these reasons, the Examiner is requested to withdraw the rejection.

IV. Rejection of Claims -- Indefiniteness

Next, the Action rejects the claims as indefinite under section 112, second paragraph.

First, all of the claims are rejected on the basis of the Examiner's contention that the term "ornamental transgenic fish" in various of the claims is unclear. While Applicants believe that the term is well known and understood in the art, to advance the case, the claims have been amended to remove the word "ornamental" and the claims are now directed to selling any such transgenic fish to the ornamental fish market.

For the record, regarding "ornamental fish," Applicants submit that such term is exceedingly well known to those of skill in the art. For example, we have enclosed page 2B of the FDA Fish Classification Guide, one of the regulatory agencies that approves the commercial distribution of transgenic ornamental fish, which provides a specific definition: "'Ornamental and aquarium' fish are defined as : fish that are produced and maintained solely for exhibit

purposes in home or public aquaria, or in ornamental garden ponds." Furthermore, specific examples of such ornamental fish are set forth in the specification at the bottom of page 22.

The Action next rejects various claims as indefinite based on the level of expression phrase in claim 1. Again, Applicants have amended claim 1 in a manner that is believe to address the concern. Thus, the claims no longer require any particular level of expression.

V. Rejection of Claims -- Obviousness

Lastly, claims 1-8, 16 and 36-41 have been rejected as obvious over the combination of Higashijima *et al.* and Bryan *et al.* (US 6,436,682).

First of all, Applicants would agree that if the transgenic fish of Higashijima *et al.* were to be sold to the ornamental fish market, then such sale would be covered by the pending claims. Thus, it is Applicants intention to cover the sale of fish such as those of Higashijima *et al.*

The question, then, is whether Bryan *et al.* would suggest the sale of "fluorescent" fish to the ornamental fish market. The answer is an unequivocal "no". Bryan teaches a wide variety of materials and objects that are to be sold as "novelty items." However, the novelty items taught by Bryan *et al.* is the sale of *inanimate* objects ("Combinations containing a first composition containing a Renilla mulleri GFP or Ptilosarcus GFP or mixtures thereof and a second composition containing a bioluminescence-generating system for use with ***inanimate articles of manufacture*** to produce novelty items are provided", col. 12, lines 35-36 (emphasis ours)) that incorporate a "bioluminescent" generating luciferase, including toys such as squirt guns and toy cigarettes, Halloween eggs, footbags, card games, finger paints, clothing, cosmetics, *etc.* (col. 12, lines 37-64). Bryan also mentions the use of fluorescent proteins for such applications as well. (col. 11, lines 26-29). It is of particular interest, however, that Bryan defines its "novelty items" as limited to "inanimate" objects, (Col. 12, lines 36), which, of course, excludes living

transgenic fish. Thus, one of ordinary skill would ***not*** read Bryan as suggesting the sale of living transgenic fish, and certainly not "fluorescent" transgenic fish.

Each of the three instances in which Bryan *et al.* mentions transgenic fish, it is only in the context of the phrase "fish food containing luciferins and transgenic fish, particularly transgenic fish that express a luciferase." (see, *e.g.*, col. 12, lines 56-58) Here, Bryan *et al.* is arguably talking about inanimate fish food that includes transgenic fish that were used to make the food. It is known that fish food is made primarily out of fish products, as evidenced by the following exemplary fish food formula:

1. Formula One Flake Food_
Fish Food Profile

Manufacturer's Brand Name: Ocean Nutrition

Ingredients: Whole Salmon, Halibut, Black Cod, Seafood Mix (including Krill, Plankton, Crab and Clams), Whole Herring, Squid, Wheat Flour, Fresh Kelp, Mysis Shrimp, Wheat Gluten, Corn Gluten, Hydrolyzed Krill, Dried Kelp, Brewer's Dried Yeast, Soybean Meal, Crayfish Digest, Potato Flour, Wheat Germ, Salmon Egg Oil, Lecithin, Beta Glucan, Potassium Sorbate, Natural Pigments (for color enhancement), Astaxanthin, Beta Carotene, Canthaxanthin, Vitamins, Amino Acids, and Trace Elements.

See http://saltaquarium.about.com/library/blank/blffiformulaoneflakes.htm. So, what Bryan *et al.* is apparently teaching is to use ground-up transgenic fish expressing luciferase in combination with the luciferase chemical substrate known as luciferin to make "inanimate" fish food, the idea being that the fish food will itself "bioluminesce" upon mastication by living fish due to the presence of the bioluminescent generation. Further evidence that Bryan *et al.* is simply disclosing transgenic fish for making fish food can be found in the fact that nowhere does Bryan *et al.* teach how to make transgenic fish – transgenic fish are only mentioned in three paragraphs, in a long laundry list along with other "inanimate" objects!

It is also significant, and an indication of the non-obviousness of the present invention, that Bryan *et al.* actually teaches that its inanimate novelty items can incorporate fluorescent proteins, which are to be "combined" with a separate "bioluminescence generating system":

> The GFPs provided herein may be used ***in combination with any suitable bioluminescence generating system***, but is preferably used in combination with a Renilla or Aequorea, Pleuromamma or Gaussia ***luciferase***.

Col. 11, lines 26-29 (emphasis ours). As can be seen from the foregoing excerpt, though, where fluorescent proteins are mentioned, they are mentioned to be used in combination with a separate bioluminescence system (*i.e.*, luciferase + luciferin). Even though fluorescent proteins in combination with luciferase systems are taught, no mention is made of *fluorescent* fish, only luciferase fish in combination with luciferin substrate. Thus, even though Bryan *et al.* were well-aware of the existence of fluorescence genes, and obviously gave great consideration of the use of fluorescence proteins in conjunction with inamimate novelty items, they only teach luciferase fish for making fish food, not fluorescent fish.

In hindsight, the reason for the foregoing is evident: food prepared with "fluorescent" (as opposed to bioluminescent) transgenic fish would not be expected to fluoresce if the fish were dead and present in fish food – only the *enzymatic* luciferin + luciferase would be expected to bioluminesce under such circumstances ("The novelty in the novelty item derives from its bioluminescence"; (Col 8 Line 36-37)). Further, by specifying that novelty derives from bioluminescence, by implication, the reader is instructed that novelty does *not* derive from fluorescence, meaning Bryan actually taught that fluorescence could *not* be employed as a novelty item, either for making fish food, or with a living fluorescent fish.

Even if one were to assume, for the sake of argument, that Bryan *et al.* would be read by one of skill as teaching the feeding of luciferin to live luciferase transgenic fish, there would still be no proper basis for maintaining an obviousness rejection. First, there is no basis in Bryan *et al.* for substituting "fluorescent" fish in place of luciferase fish: due to the underlying biochemical differences between "fluorescence" and "bioluminescence" discussed above, the

feeding of *luciferin* food to *fluorescent* fish would not lead to any bioluminescence, and thus would be contrary to the stated goal of Bryan *et al.* to provide luciferin fish food as an inanimate novelty item. Thus, there would be no motivation to substitute fluorescent fish for Bryan *et al.*'s luciferase fish. Furthermore, since luciferin fish food would not cause fluorescent fish to bioluminesce, the proposed combination would inconsistent with the teachings of Bryan *et al.* As the Board stated in *Ex parte Hartmann*, 186 USPQ 366, 367 (PTO Bd. App. 1974), "[r]eferences cannot be properly combined with each other when such would result in destroying that on which the invention of one of the references is based."

The distinction between "fluorescence" of the present invention and the "bioluminescence" as provided by luciferin is particularly noteworthy. Bioluminescence is a phenomenon whereby light is produced ***directly*** by a chemical reaction, without the presence of an external light source:

> Bioluminescence is the production and emission of light by a living organism as the result of a chemical reaction during which chemical energy is converted to light energy. The name originates from the Greek *bios* for "living" and the Latin *lumen* "light". Bioluminescence may be generated by symbiotic organisms carried within a larger organism. It is generated by an enzyme-catalyzed chemoluminescence reaction, wherein the pigment luciferin is oxidised by the enzyme luciferase. Adenosine triphosphate (ATP) is involved in most instances. The chemical reaction can occur either within or outside of the cell. In bacteria, the expression of genes related to bioluminescence is controlled by an operon called the lux operon.

Wikipedia definition of "Bioluminescence," http://en.wikipedia.org/wiki/Bioluminescent. Bioluminescence requires the interaction of a chemical substrate, such as luciferin, and an enzyme, such as luciferase.

"Fluorescence", on the other hand, does not require the addition of an external chemical substrate, but instead involves simply altering one wavelength of light to another wavelength – so, it requires a light source, not a chemical substrate:

> Fluorescence is a luminescence that is mostly found as an optical phenomenon in cold bodies, in which the molecular absorption of a photon triggers the emission of another photon with a longer wavelength. The energy difference between the absorbed and emitted photons ends up as molecular vibrations or heat. Usually the absorbed photon is in the ultraviolet range, and the emitted light is in the visible range, but this depends on the absorbance curve and Stokes shift of the particular fluorophore. Fluorescence is named after the mineral fluorite, composed of calcium fluoride, which exhibits this phenomenon.

Wikipedia, at http://en.wikipedia.org/wiki/Fluorescence. In the Background section, Bryan *et al.* recognizes the distinction between fluorescence and bioluminescence ("Luminescence includes fluorescence, phosphorescence, chemiluminescence and bioluminescence. (Col 1 line 67 – Col 2 line 1)).

Thus, in contrast to the use of a bioluminescent substrate + enzyme as taught by Bryan *et al.*, the fluorescent fish of the present invention do not require fish food with the proper mix of luciferase and luciferins to produce a luminescent effect – all ***our*** fish require is the addition of a light source! It was the present inventors who, for the first time, taught to produce and sell *fluorescent* fish to the ornamental fish market. It is the hallmark of invention, and the inventive process, to provide what may appear to be simple solutions to overcome shortcomings in the "tried and true" prior art approaches. Thus, the present inventors chose a path distinct from Bryan *et al.* – and indeed actually taught away from by Bryan *et al.* – to solve the problem of having to provide a separate chemical substrate to achieve a novel effect!

We submit, therefore, that Bryan *et al.* actually supports a conclusion of *non-obviousness* by teaching merely fish food that would create a bioluminescent effect – failing to recognize the value of creating and marketing fluorescent fish to the ornamental fish market. The present inventors have therefore provided their fish using an approach rejected by Bryan *et al.* It must be remembered that persons of ordinary skill always trod down "tried and true" paths. They do not seek to innovate or provide solutions that are not specifically suggested in the existing art. As

has long been observed by the Court of Appeals for the Federal Circuit, one of ordinary skill "is presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate." *The Standard Oil Company v. American Cyanamid Co.*, 774 F.2d 448, 227 USPQ 293 (Fed. Cir. 1985).

Thus, we submit that one of ordinary skill, reading Bryan *et al.*, would not at all be enlightened to sell the fish of Higashijima *et al.* to the ornamental fish market – they would, at best, instead be expected to follow the teachings of Bryan *et al.* to sell bioluminescent fish in combination with a bioluminescent substrate such as luciferin.

Thus, for the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the obviousness rejections.

VI. Conclusion

It is submitted that by the foregoing it can be seen that the rejections have been overcome. The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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